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Novel asymmetric azaquinolizinium monomethine cyanine dyes versus a Thiazole Orange analog: a comparison of photophysical and dsDNA binding properties

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New asymmetric monomethine cyanine dyes containing an azaquinolizinium core have been synthesized using novel 4-chloropyridopyrimidinium chlorides as building blocks. The photophysical properties of the dyes have been compared to those of a novel monomeric tricationic Thiazole Orange (TO) analog. Compounds **8** and **13** have very low fluorescence in TE buffer in the absence of dsDNA, but after binding to dsDNA a dramatic increase in the fluorescence intensity was observed. Computational tools (DFT and TDDFT calculations) have been employed in studying the relationship between the chemical structure and the optical properties of the chromophores.

Keywords: cyanine dyes, DNA, fluorescence, azaquinolizinium salts, Thiazole Orange.

INTRODUCTION

Asymmetric cyanine dyes have attracted considerable interest due to their excellent nucleic acid staining properties. In the absence of DNA, such dyes have negligible fluorescence but upon binding to biomolecule they usually exhibit a large enhancement of the fluorescence intensity [1]. As a result, cyanine dyes are widely used as fluorophores for DNA detection and visualization in various applications [2–4]. A wide range of novel examples with similar properties based mainly on TO and Oxazole Yellow (YO) have been designed, synthesized and commercialized [5, 6]. In this scientific area two general strategies for discovering more efficient fluorescent nucleic acid stains have been used. The first approach is to improve the already well known bio-labels. The second approach is to design and create new types of fluorophores based on novel heterocyclic compounds. As an extension of our previous studies on the synthesis and exploration of the properties of new nucleic acid fluorescent stains [7], we report here a synthetic route for the preparation of new asymmetric azaquinolizinium monomethine cyanine dyes and compare their photophysical properties with those of a new tricationic analog of TO. Computational tools are employed in an effort to understand the relationships between the chemical structure and the optical properties of the fluorochromes.

EXPERIMENTAL

All solvents used in the present work were HPLC grade and commercially available. Column chromatography was performed on Silica gel 60, pore size 60 Å, 230–240 mesh, 40–63 μm particle size (Fluka). The starting materials **1a**, **1b**, **2** and **3** are commercially available and they were used as supplied. Melting points were determined on a Büchi MP B-545 apparatus and are uncorrected. NMR spectra were obtained on a Bruker Avance II+ 600 spectrometer in $CDCl_3$ and on a Bruker III HD Avance-500 spectrometer in DMSO-d_6. UV-vis spectra were measured on a Unicam 530 UV-VIS spectrophotometer and the fluorescence spectra were obtained on a Cary Eclipse fluorescence spectrophotometer (Varian, Australia). Intermediates **7** and **9** were synthesized by methods described in the

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literature [8]. Details about the synthesis and the purification of dye **13** will be published elsewhere.

Synthesis of 2,2-dimethyl-5-((pyridin-2-ylamino) methylene)-1,3-dioxane-4,6-dione (4a) and 5-(((4-bromopyridin-2-yl)amino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (4b)

A mixture of 2-aminopyridine (**1a**) or 4-bromo-2-aminopyridine (**1b**) (10 mmol), Meldrum's acid (1.1 equiv. toward **1a** or 1.25 equiv. toward **1b**) and triethyl orthoformate (12 ml) was stirred at 100°C for 30 min. The excess of triethyl orthoformate was evaporated under reduced pressure. The crude product was purified by recrystallization from methanol (**4a**) or recrystallization from chloroform (**4b**). **4a:** Yield 93%, ^{1}H-NMR (δ (ppm), $CDCl_3$, 600 MHz): 1.76 (s, CH_3, 6H); 7.04 (dt, CH, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 0.7 Hz, 1H); 7.18 (ddd, CH, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 4.9 Hz, $^4J_{HH}$ = 0.8 Hz, 1H); 7.76 (ddd, CH, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 7.5 Hz $^4J_{HH}$ = 1.9 Hz, 1H); 8.42 (dd, CH, $^3J_{HH}$ = 4.8 Hz, $^4J_{HH}$ = 1.0 Hz, 1H); 9.42 (d, CH, $^3J_{HH}$ = 13.5 Hz, 1H); 11.30 (d, NH, $^3J_{HH}$ = 12.8 Hz, 1H). **4b:** Yield 93%, ^{1}H-NMR (δ (ppm), $CDCl_3$, 600 MHz): 1.76 (s, 6H, CH_3); 7.27 (d, 1H, $^4J_{HH}$ = 0.6 Hz); 7.33 (dd, 1H, CH, $^3J_{HH}$ = 5.3 Hz, $^4J_{HH}$ = 0.8 Hz); 8.24 (d, 1H, CH, $^3J_{HH}$ = 5.3 Hz); 9.38 (d, 1H, CH, $^3J_{HH}$ = 13.3 Hz); 11.27 (d, 1H, NH, $^3J_{HH}$ = 13.0 Hz).

Synthesis of 4H-pyrido[1,2-a]pyrimidin-4-one (5a) and 8-bromo-4H-pyrido[1,2-a]pyrimidin-4-one (5b)

A mixture of **4a** (3 mmol) or **4b** (3 mmol) and *Dowtherm A* (20 ml) was refluxed for 30 min. The reaction mixture was filtered through silica and washed with hexane to remove *Dowtherm A* and the compound was eluted with ethyl acetate (**5a**) or dichloromethane/ethyl acetate (**5b**). **5a**: Yield 90%, Mp: 129–130°C (from methanol); ^{1}H-NMR (δ (ppm), $CDCl_3$, 600 MHz): 6.47 (d, CH, $^3J_{HH}$ = 6.3 Hz, 1H); 7.19 (td, CH, $^3J_{HH}$ = 7.0 Hz, $^3J_{HH}$ = 1.3 Hz, 1H); 7.69 (d, CH, $^3J_{HH}$ = 8.9 Hz, 1H); 7.77 (ddd, CH, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.5 Hz, 1H); 8.31 (d, CH, $^3J_{HH}$ = 6.3 Hz, 1H); 9.10 (d, CH, $^3J_{HH}$ = 7.1 Hz, 1H). **5b**: Yield 87%. ^{1}H-NMR (δ (ppm), $CDCl_3$, 600 MHz): 6.44 (d, CH, $^3J_{HH}$ = 6.4 Hz, 1H); 7.23 (dd, CH, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 2.1 Hz, 1H); 7.85 (dd, CH, $^4J_{HH}$ = 2.1 Hz, $^5J_{HH}$ = 0.7 Hz, 1H); 8.25 (d, CH, $^3J_{HH}$ = 6.4 Hz, 1H); 8.90 (dd, CH, $^3J_{HH}$ = 7.6 Hz, $^5J_{HH}$ = 0.7 Hz, 1H).

Synthesis of 4-chloropyrido[1,2-a]pyrimidin-5-ium chloride (6a) and 8-bromo-4-chloropyrido[1,2-a] pyrimidin-5-ium chloride (6b)

To a solution of **5a** (1 mmol) or **5b** (1 mmol) in dichloromethane were added phosphoryl chloride (5 mmol) and DMF (1 drop). The reaction mixture was refluxed and stirred vigorously under argon for 4 h. Then was allowed to cool down to room temperature and diethyl ether (40 mL) was added. The resulting precipitate was filtered and dried in a desiccator. The target compounds **6a** and **6b** are highly hygroscopic and unstable. They were used in the next step without further purification. **6a:** Yield 95%; **6b:** Yield 98%.

Synthesis of 4-((4H-pyrido[1,2-a]pyrimidin-4-ylidene)methyl)-1-benzylquinolin-1-ium iodide (8) and 2-((8-bromo-4H-pyrido[1,2-a]pyrimidin-4-ylidene)methyl)-3-(3-(pyridin-1-ium-1-yl)propyl) benzo[d]thiazol-3-ium iodide (10)

Compound **6a** (1 mmol) or **6b** (1 mmol) and an appropriate quaternary ammonium salt **7** or **9** (1.2 mmol) were finely ground in a mortar and the mixture was transferred to a 50 ml reaction flask, equipped with a condenser and an electromagnetic stirrer. The flask was flushed with argon and methanol (10 mL) was added. The reaction mixture was heated at 50°C for 5 min and DIPEA (2.1 mmol) was added dropwise. Then the mixture was stirred at room temperature for 2 h and the resulting precipitate was filtered off and air dried. The target dyes were purified by flash column chromatography (dichloromethane/methanol mixture of increasing polarity up to 10/1) and subsequently crystallized from methanol/diethyl ether = 1/3. **8:** Yield 82%, Mp: 174–175°C; ^{1}H-NMR (δ(ppm), DMSO-d_6, 500 MHz): 5.74 (d, $^3J_{HH}$ = 22.0 Hz, CH, 1H), 5.81 (s, CH_2, 2H), 6.31 (brs, CH, 1H), 7.25–7.43 (m, CH, 9H), 7.59–7.63 (m, CH, 2H), 7.75–7.71 (m, CH, 2H), 7.84 (m, CH, 1H), 8.09 (brs, CH, 2H). ^{13}C-NMR (δ (ppm), DMSO-d_6, DEPT 135 MHz): 56.7 (CH_2), 109.13 (CH), 109.69 (CH), 118.55 (CH), 126.59 (CH), 126.69 (CH), 126.99 (CH), 127.05 (2CH), 126.52 (CH), 128.41 (CH), 128.55 (CH), 129.51 (2CH), 129.53 (CH), 129.66 (CH), 129.76 (CH), 133.20 (CH), 144.09 (CH). Elemental analysis for $C_{25}H_{20}IN_3$ (Mw = 489.07) C(%): Calculated 61.36; Found 60.92; H(%) Calculated 4.12; Found 4.00; N (%): Calculated 8.59; Found 8.73. **10:** Yield 41%, Mp: 251–251°C; ^{1}H-NMR (δ(ppm), DMSO-d_6, 500 MHz): 1.22–1.26 (m, CH_2, 2H), 2.61–2.68 (m, NCH_2, 2H), 4.51 (brs, N^+CH_2, 2H), 6.42 (s, CH, 1H), 7.19–7.22 (m, CH, 3H), 7.43–7.48 (m, CH, 2H), 7.59–7.64 (m, CH, 4H), 7.86 (brs, CH, 1H), 8.09 (brs, CH, 2H), 8.25–8.83 (m, CH, 2H). ^{13}C-NMR (δ (ppm), DMSO-d_6, DEPT 135 MHz): 29.59 (CH_2), 57.97 (NCH_2), 57.98 (N^+CH_2), 113.22 (CH), 125.22 (CH), 125.83 (CH), 128.52 (CH), 128.54 (CH), 128.57 (CH), 128.63 (CH), 128.69 (CH), 145.21 (CH), 150.23 (CH), 153.20 (CH), 153.79 (CH), 153.88 (CH), 171.12 (CH), 175.41 (CH). Elemental

analysis for $C_{24}H_{21}BrI_2N_4S$ (Mw = 729.88) C(%): Calculated 39.42; Found 39.48; H(%): Calculated 2.89; Found 2.67; N (%): Calculated 7.66, Found 7.82.

COMPUTATIONAL

The molecular ground state geometries of the cationic fragments of **8**, **10** and **13** with/without Cl^- counterions were fully optimized using B3LYP [9, 10] functional. The diffuse function-augmented 6–31G(d,p) [11–13] basis set was adopted for all atoms. C_1 symmetry was assumed for all systems and default convergence criteria were used; local minima were verified by establishing that the Hessians had zero negative eigenvalues. The structures with counterions were optimized in methanol by using IEFPCM (Integral Equation Formalism Polarizable Continuum Model) [14] method. TDPBE0/6–311+G(2d,p) calculations were performed to compute the 20 lowest excited states of each structure. Solvent effects were included in TDDFT calculations (via IEFPCM). All calculations were performed using Gaussian 09 [15]. The PyMOL molecular graphics system was used to generate the molecular graphics images [16].

RESULTS AND DISCUSSION

The 4*H*-pyrido[1,2-*a*]pyrimidin-4-one scaffold is a privileged structure [17–19] in medicinal chemistry. In general this compound is synthesized from 2-aminopyridine using β-diesters as ring-closure reagents (such as *Meldrum's* acid, for example) [20–25].

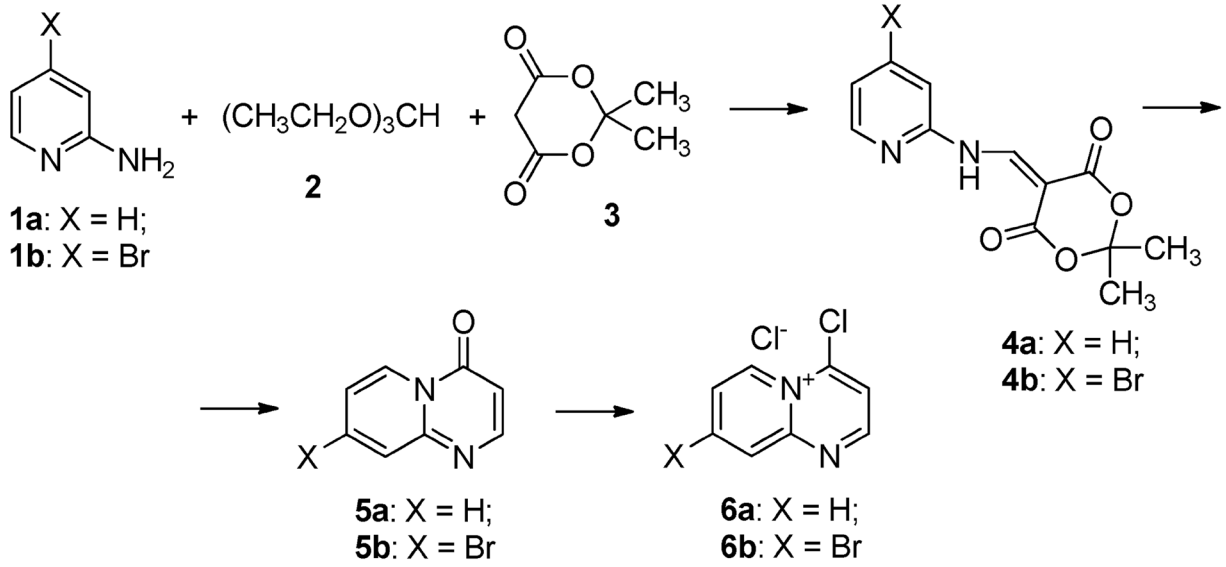
Applying reaction conditions modified by us [26–29], the 4*H*-pyrido[1,2-*a*]pyrimidin-4-one derivatives **5a** and **5b** were prepared in high yields and their structures were confirmed by NMR spectroscopy (Scheme 1).

The chlorination of intermediates **5a** and **5b** in DCM in the presence of DMF as a catalyst (Scheme 1) furnished the target 4-chloropyridopyrimidinium salts **6a** and **6b** in excellent yields (Scheme 2).

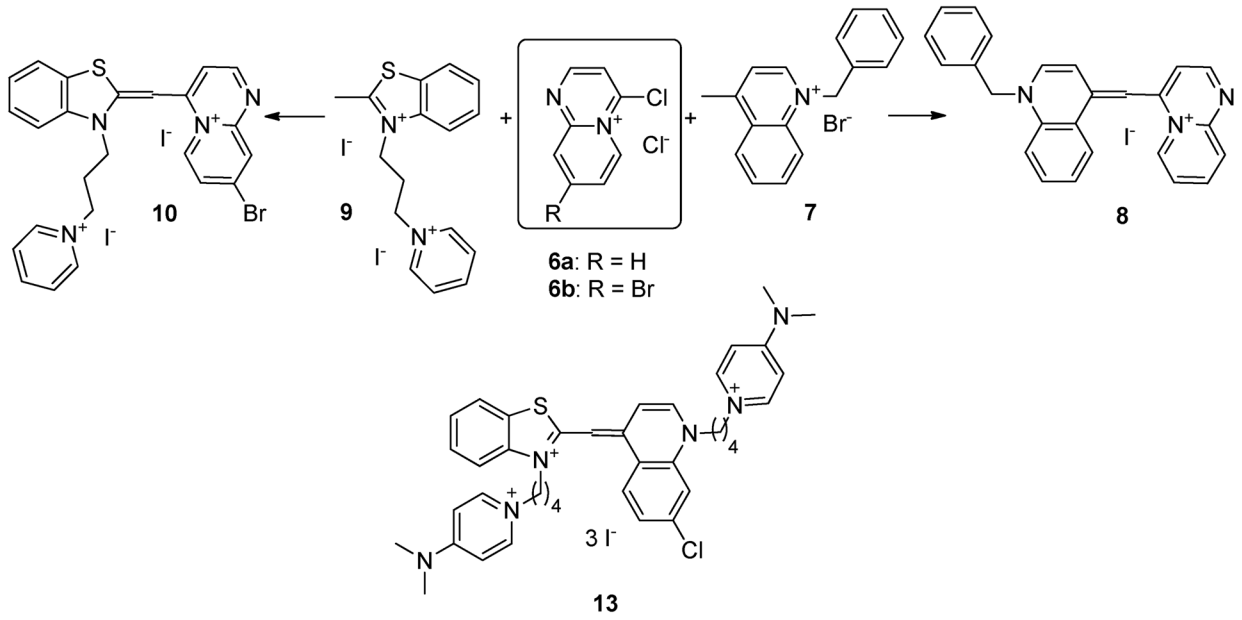
Monomethine cyanine dyes such as TO or its analogs can be synthesized according to Brooker's method [2, 30–33], running along with side reactions and including the evolution of methyl mercaptan (methanethiol) – the toxic by-product with a very unpleasant odor [34]. In an effort to avoid these problems, the azaquinolizinium dyes **8** and **10** and the novel tricationic TO analog **13** (Scheme 2) were synthesized by an environmentally more benign method that was successfully applied previously by our group [35–37].

The newly synthesized cyanine dyes **8**, **10** and **13** were characterized by NMR and UV-VIS spectroscopy and by elemental analysis.

The photophysical properties of dyes **8** and **10** were evaluated and the data were compared to those of the new tricationic TO analog **13**. Three absorption bands were observed for a methanol solution of dye **8** at wavelengths of 562 nm, 590 nm and 710 nm and these can be associated with different types of aggregates [38]. Similar behavior was observed for a methanol solution of dye **10** (Fig. 1A) with a hypsochromically shifted shoulder (H-aggregates) toward the main absorption signal.



Scheme 1



Scheme 2

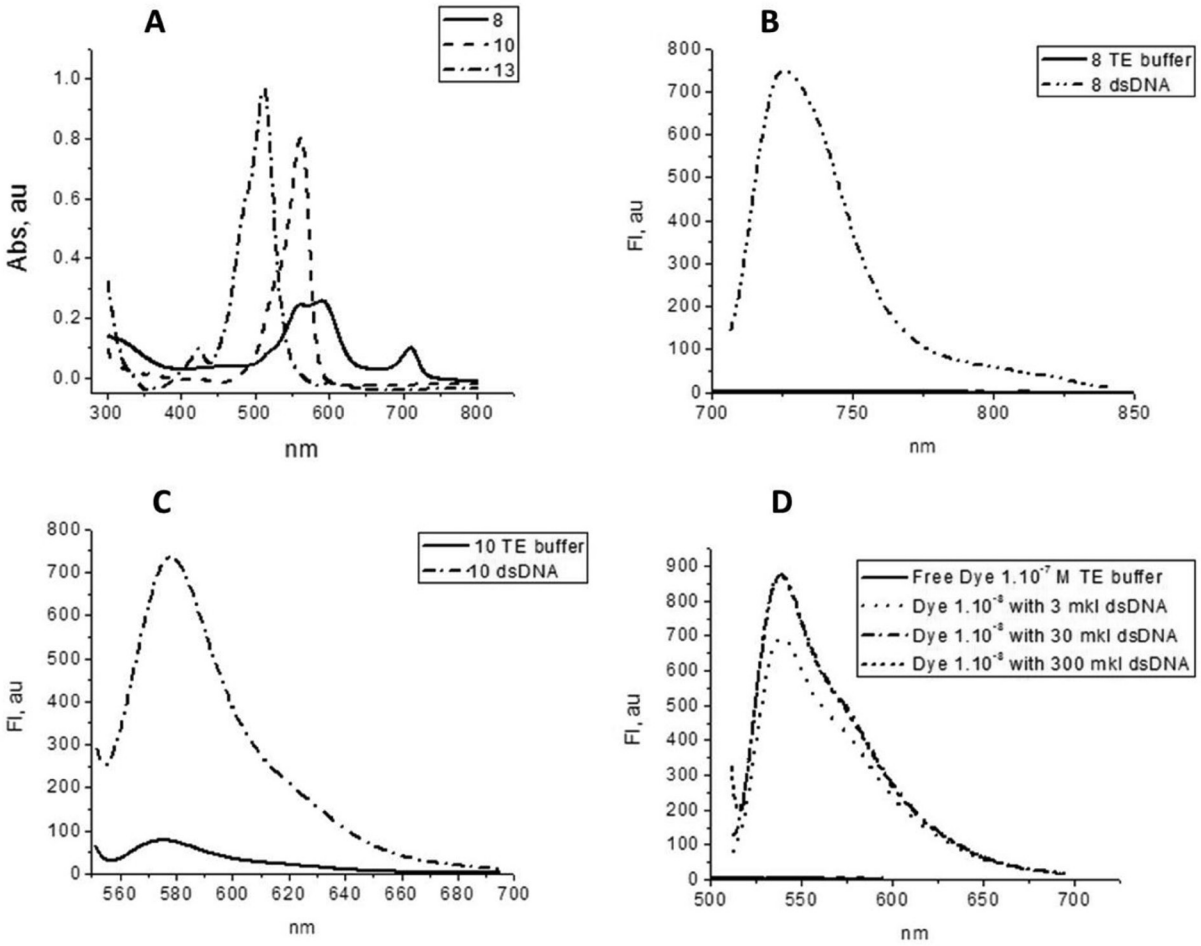


Fig. 1. (A) Absorption spectra of dyes **8**, **10** and **13** in methanol (1.10^{-5} M); (B) Increase in the fluorescence of dye **8** in the presence of dsDNA in TE buffer solution; (C) Change in the fluorescence of dye **10** in TE buffer in the presence of dsDNA; (D) Fluorescence of free dye **13** in TE buffer and varied concentration of dsDNA.

Table 1. Photophysical properties of dyes 8, 10 and 13 in methanol and in TE buffer in the absence and in the presence of dsDNA

Dye	Absorption			Fluorescence				
	Abs[a]	Abs[b]	Abs[c]	λ_{max} [d]	I_{fl0} [d]	λ_{max} [e]	I_{fl} [e]	Ratio I_{fl}/I_{fl0}
8	562 (24 500)	556	561	598	22	-----	-----	----
	590 (25 600)			629	1.6	-----	-----	-----
	710 (9 960)	706	710	718	0.6	726	750	1250
10	562 (80 600)	559	567	578	51	578	734	14
13	513 (97 000)	513	521	538	4.3	538	875	203

[a] λ_{max} (nm) and molar absorptivity ε ($l.mol^{-1}.cm^{-1}$) of free dyes in methanol; [b] λ_{max} (nm) of free dye in TE buffer; [c] λ_{max} (nm) of dye-dsDNA complex in TE buffer; [d] λ_{max} (nm) and I_{fl0} of free dye in TE buffer; [e] λ_{max} (nm) and I_{fl} of complex dye-dsDNA in TE buffer.

The absorption spectrum of dye **8** in TE buffer in the absence of DNA contains two peaks at 556 nm and 706 nm and these are shifted bathochromically to 561 nm and 710 nm, respectively, in the same buffer in the presence of dsDNA (Table 1). A bathochromic shift of the absorption signal for dye **10** was observed in TE buffer from 559 nm for the free dye to 567 nm in the presence of dsDNA (Table 1). These effects provide evidence for intercalation, as reported in other investigations into cyanine dyes [39].

Dye **8** shows three fluorescence bands in TE buffer. Fluorescence was not observed in the presence of dsDNA in the buffer solution upon excitation at the shorter wavelength bands (598 nm and 629 nm). The longest wavelength fluorescence band of **8** at 718 nm is characterized by very low intrinsic fluorescence intensity, but excitation at 718 nm in the presence of dsDNA led to a dramatic increase in the fluorescence intensity by up to 1250-fold (Table 1). Dye **10** showed a similar to **8** change in the fluorescence intensity in the presence of dsDNA, but its very high fluorescence in the free state does not make it suitable as a fluorescent label for dsDNA detection. Dye **13** showed an even higher fluorescence intensity in the presence of dsDNA, but its intrinsic fluorescence (4.3 au, Table 1) led to a decrease in the ratio I_{fl}/I_{fl0} (Table 1). One probable explanation for the observed photophysical properties of compound **13** is that the presence of the halogen substituent connected to the chromophore leads to an increase in the hydrophobicity and thus to the formation of fluorescent aggregates in the TE-buffer solution.

The TDDFT method was used to generate the absorption spectra of the cationic fragments of dyes **8**, **10** and **13 (**presented in Fig. 2 with the respective atom color scheme**)** with Cl^- counterions optimized in methanol.

TDPBE0/6-311+G(2d,p) calculations in methanol predicted absorption maxima at 482 nm, 450 nm and 466 nm for **8**, **10** and **13**, respectively; a typical systematic overestimation of the excitation energies by the TDDFT schemes was observed [40]. It can be proposed that different dimers may originate from **8**; data for the most stable dimer are presented in Table 2 and the optimized structure of this dimeric form is represented in Fig. 3.

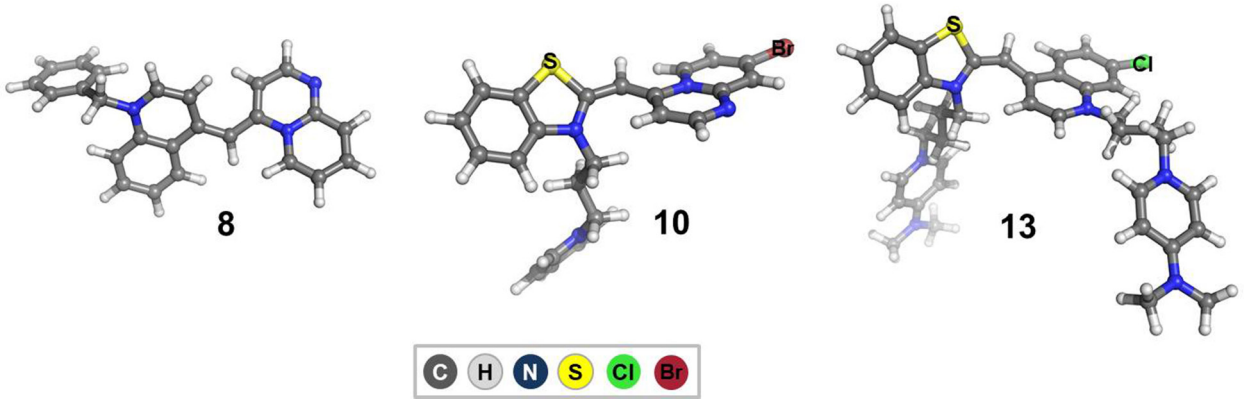


Fig. 2. B3LYP optimized structures of the cations of dyes **8**, **10** and **13**.

Table 2. TDPBE0/6-311+G(2d,p) calculated excitation wavelengths, λ (nm), and oscillator strengths, f, of the cationic fragments of dyes **8**, **10** and **13** with Cl^- counterions in methanol

Compound	λ	f
8	482	0.8798
	431	0.0590
8_dimer	502	0.0202
	496	0.1692
	486	0.1137
	475	1.1770
	426	0.0565
10	450	0.7059
	423	0.1029
13	466	0.9049

Simulated with a Gaussian broadening with a full width at half-maximum (fwhm) 0.06–0.07 eV and a height proportional to the oscillator strength for each transition spectra are presented in Figure 3. At this broadening the **8_dimer** spectrum qualitatively reproduced the splitting in the experimental absorption spectrum of dye **8** in methanol solution, i.e., the monomer-dimer equilibrium of dye **8** can be hypothesized.

CONCLUSION

Three novel dyes were synthesized and their photophysical properties were investigated. Two of the dyes (**8** and **13**) possess typical features of fluorescent DNA labels. In the absence of DNA, these dyes have negligible fluorescence, but after binding to DNA a dramatic increase in the fluorescence intensity was observed. Dye **8** is worth highlighting because excitation at 706 nm led to a significant (1250-fold) increase in the fluorescence in the presence of dsDNA. Computational tools were employed in an effort to understand the relationship between the chemical structure and the optical properties of the chromophores. The results are

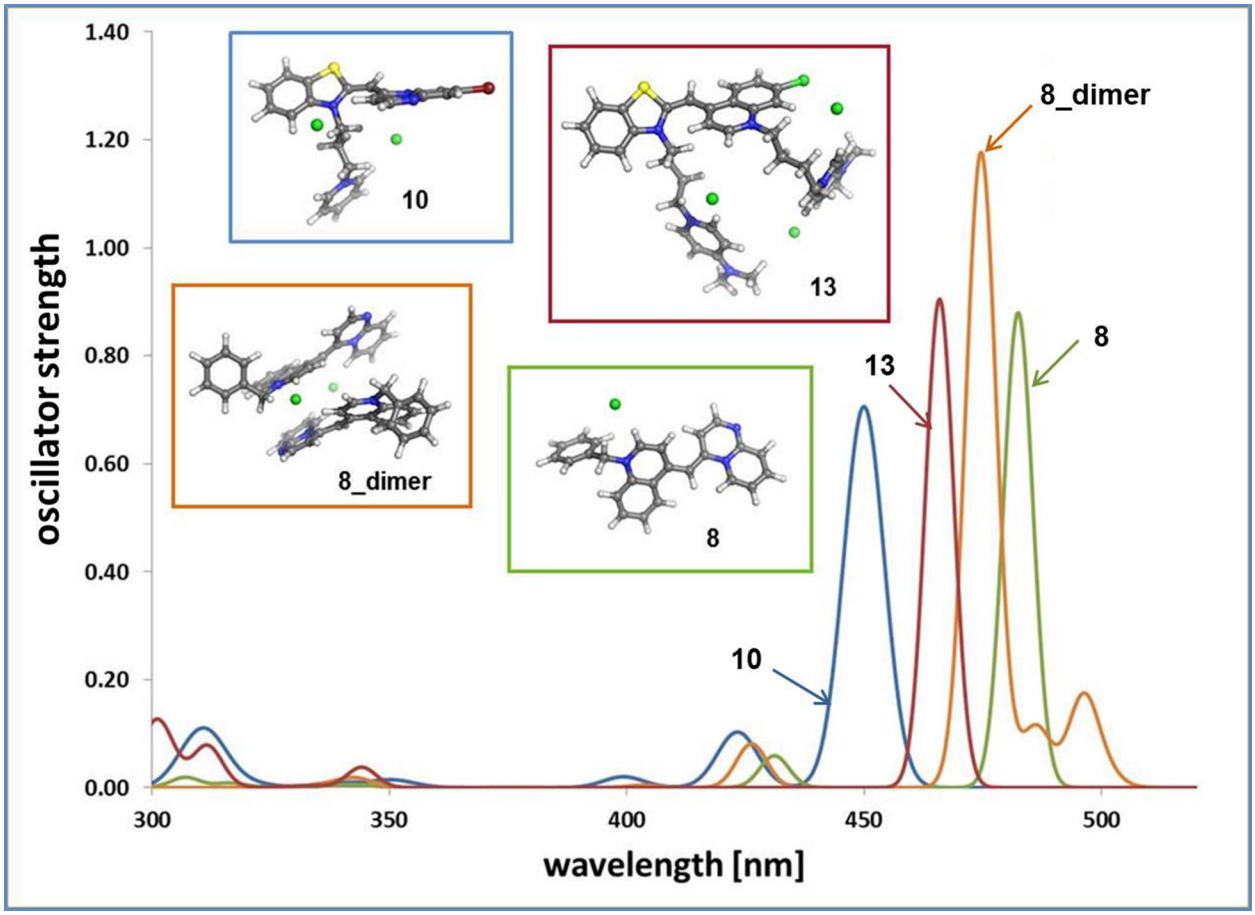


Fig. 3. TDPBE0/6-311+G(2d,p) simulated spectra of the cationic fragments of dyes **8** (monomer and dimer), **10** and **13** with Cl^- counterions in methanol.

promising and warrant further investigations into the newly synthesized dyes as fluorogenic labels for DNA analysis in research and medical science. Additional quantum-chemical calculations, including the simulation of fluorescence spectra of new azaquinolizinium heterocycle-containing dyes, subsequent design of new analogs and further experiments in order to examine their DNA binding mechanism are planned.

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СРАВНЯВАНЕ НА ФОТОФИЗИЧНИТЕ И ДНК-СВЪРЗВАЩИ СВОЙСТВА НА НОВИ АСИМЕТРИЧНИ АЗАХИНОЛИЗИНИЕВИ МОНОМЕТИНОВИ ЦИАНИНОВИ БАГРИЛА С НОВ АНАЛОГ НА ТИАЗОЛ ОРАНЖ

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(Резюме)

Синтезирани са нови асиметрични монометинови цианинови багрила, съдържащи азахинолизиниев фрагмент, с използването на 4-хлоропиридопиримидиниеви хлориди като изходни съединения. Фотофизичните свойства на багрилата са сравнени с тези на нов мономерен трикатионен аналог на Тиазол Оранж (ТО). Съединения 8 и 13 се характеризират с много ниска собствена флуоресценция в ТЕ буфер в отсъствие на двДНК, но след свързване с двДНК се наблюдава значително увеличение на интензитета на флуоресценцията им. Изчислителни методи (DFT и TDDFT изчисления) са използвани за изследване на връзката между химичната структура и оптичните свойства на хромофорите.